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(54) PROCEDE DE PRODUCTION DE DOSES SOLIDES
(54) PROCESS FOR PRODUCING SOLID DOSAGE FORMS

(57)

The present invention relates to a process for producing solid dosage forms by mixing at least one polymeric binder, where appropriate at least one active ingredient and, where appropriate, conventional additives to form a plastic mixture, using polyamides with sulfonate groups as polymeric binder.

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(54) **PROCEDE DE PRODUCTION DE DOSES SOLIDES**
(54) **PROCESS FOR PRODUCING SOLID DOSAGE FORMS**

(57) The present invention relates to a process for producing solid dosage forms by mixing at least one polymeric binder, where appropriate at least one active ingredient and, where appropriate, conventional additives to form a plastic mixture, using polyamides with sulfonate groups as polymeric binder.

Abstract

The present invention relates to a process for producing solid dosage forms by mixing at least one polymeric binder, where appropriate at least one active ingredient and, where appropriate, conventional additives to form a plastic mixture, using polyamides with sulfonate groups as polymeric binder.

Process for producing solid dosage forms

The invention relates to a process for producing solid dosage forms by mixing at least one polymeric binder and, where appropriate, at least one active ingredient and, where appropriate, conventional additives to form a plastic mixture, and shaping. The invention particularly relates to a process for producing solid pharmaceutical forms.

Classical processes for producing solid pharmaceutical forms, especially tablets, are carried out batchwise and comprise a plurality of stages. Pharmaceutical granules represent an important intermediate therefor. Thus, for example, it is disclosed in the book "Pharmazeutische Technologie", authors Prof. Bauer, Frömmig and Führer, Thieme Verlag, pages 292 et seq., that drug forms can be obtained from the melts by dry granulation. The possibility of producing solidified melt granules either by melting and shock solidification, by casting and comminuting or by prilling in spray towers is described. One problem with these processes is the accurate shaping which is necessary for producing drugs. Irregular particles or fragments are frequently produced so that the resulting shape by no means corresponds to customary drug forms, and granules therefore have only little importance as a drug form on their own. Production of desired solid drug forms requires the use of further process steps such as compression in tabletting machines. This is time-consuming and costly.

A considerably simpler continuous process for producing solid pharmaceutical forms has been known for some time and entails extruding a solvent-free melt of a polymeric binder containing active ingredients, and shaping this extrudate to the required drug form, for example in a calender with molding rolls, see EP-A-240 904, EP-A-240 906 and EP-A-337 256 and EP-A-358105. It is possible in this way to achieve specific shaping. The polymeric binders employed are, in particular, polymers of N-vinylpyrrolidone or copolymers thereof, e.g. with vinyl acetate.

The use of polyamides in medical technology and pharmacy is known to the skilled worker. Implants, the transdermal administration of medicinal substances, dialysis membranes and drug coatings represent only a few examples from the versatile application areas for polyamides.

WO 96/21427 A1 describes, for example, the possibility of employing polyamides as biodegradable, water-insoluble, polyamide-containing copolymers in liquid drug formulations with controlled release of active ingredient. These polymers contain the active ingredient in dissolved, dispersed or suspended form.

The use of polyamides in solid pharmaceutical compositions is mentioned in WO 93/24154 A1. These compositions are based on melt-spun polymers whose predominantly amorphous nature is intended to ensure rapid and constant release of active ingredient.

A process for producing medicinal pills and tablets is described in DE-A-1 766 546. This involves a shaping step in which the carrier substance is converted into a melt containing the active ingredient in dispersed and/or dissolved form, this melt is placed in the trough-like space of a pair of rotating rolls, the rolls being provided on their outer surfaces with cavities to receive the coating composition and being cooled in order to allow the liquid coating composition to solidify in cavities, and the medicinal products obtained in this way leave the cavities. The carrier substance may also comprise thermoplastics such as polyvinyl chloride, polyethylene, polypropylene, polyamides, polystyrene, polyvinylidene chloride, acrylonitrile/butadiene/styrene or acrylonitrile/styrene.

Polyamide-containing compositions with delayed release of active ingredient are mentioned in EP 381 445 A2 and EP 381 446 A1. These comprise topical compositions for dental or oral treatment in which the respective active ingredient is embedded in cellulose or a hydrophobic polymer.

Polymers with sulfonate groups are described in DE 40 37 518 A1 as suitable component for producing particular resin particles with a narrow size distribution and essentially spherical shape. Resin particles of this type can be used in particular for electrophotographic toners. A use as carrier for medicinal products is mentioned in passing.

However, the production of the above compositions is in many cases very complicated and thus time-consuming and costly and, in most cases, results in dosage forms with rapid release characteristics.

It is an object of the present invention to provide a simple and low-cost process for producing solid dosage forms, especially drug forms, with delayed release of active ingredient.

We have found that this object is achieved by producing the dosage forms by melt extrusion and, moreover, using polyamides with sulfonate groups as binders.

The present invention therefore relates to a process for producing solid dosage forms by mixing at least one polymeric binder, where appropriate at least one active ingredient and, where appropriate, conventional additives to form a plastic mixture, and shaping, wherein polyamides with sulfonate groups are used as polymeric binders.

The novel process makes it possible to produce solid dosage forms in a simple and low-cost manner. The advantageous properties of the polyamides with sulfonate groups are not impaired by the conversion into the plastic state. In addition, the novel process surprisingly results in dosage forms with very slow release of active ingredient (slow release formulations), whereas the polyamides previously used resulted in dosage forms with rapid release of active ingredient. It is thus possible to achieve any required release profiles by admixtures with rapid-release auxiliaries. In addition, owing to the high glass transition temperature, it is possible to produce hard, tack-free dosage forms which have good storage stability even at high temperatures.

Dosage forms mean herein all forms which are suitable for use as drugs, plant treatment compositions, human and animal foods and for delivering fragrances and perfume oils. These include, for example, tablets of any shape, pellets, granules, but also larger forms such as cubes, blocks (bricks) or cylindrical forms, which can be used, in particular, as human or animal foods.

The dosage forms obtainable according to the invention generally comprise:

a) 0 to 90% by weight, in particular 0.1 to 60% by weight (based on the total weight of the dosage form) of an active ingredient,

b) 10 to 100% by weight, in particular 40 to 99.9% by weight, of a polymeric binder and

c) where appropriate additives.

If the dosage form is employed for human or animal food purposes, the active ingredient may be absent, i.e. the dosage form may comprise up to 100% of the polymeric binder.

The polymeric binders used according to the invention are polyamides with sulfonate groups. The sulfonate groups can be introduced with one or more of the monomers employed to construct the polyamides. Moreover these monomers may have one or more sulfonate groups. The molar proportion of monomers with sulfonate groups is, as a rule, at least 0.5 mol% and preferably not more than 50 mol%. 5 to 35 mol% are particularly preferred, especially 10 to 30 mol%.

Dicarboxylic acids with sulfonate groups are particularly suitable for constructing the polyamides employed according to the invention. If other dicarboxylic acids besides these dicarboxylic acids with sulfonate groups are used, the ratio of the molar proportions of dicarboxylic acids with sulfonate groups to other dicarboxylic acids is, as a rule, 1:99 to 99:1, preferably 10:90 to 70:30 and, in particular, 20:80 to 60:40.

The polyamides with sulfonate groups which are preferably used are obtainable from

A1) 0 to 90 mol% of at least one monoamino carboxylic acid, the lactam thereof or monoamino carboxylic acid/lactam mixtures,

A2) 5 to 50 mol% of at least one primary or secondary diamine,

A3) 0.5 to 49.5 mol% of at least one dicarboxylic acid with sulfonate groups and, where appropriate,

A4) 0.5 to 49.5 mol% of at least one other dicarboxylic acid, where the total of the molar proportions of monomers A3) and A4) essentially corresponds to the molar proportion of monomer A2).

It is particularly preferred to use polyamides with sulfonate groups which are obtainable from

A1) 0 to 50 mol% of at least one monoamino carboxylic acid, the lactam thereof or monoamino carboxylic acid/lactam mixtures,

A2) 45 to 50 mol% of at least one primary or secondary diamine,

A3) 5 to 35 mol% of at least one dicarboxylic acid with sulfonate groups and, where appropriate,

A4) 15 to 45 mol% of at least one other dicarboxylic acid, where the total of the molar proportions of monomers A3) and A4) essentially corresponds to the molar proportion of monomer A2).

Very particularly preferred polyamides with sulfonate groups are obtainable from

A1) 0 to 45 mol% of at least one monoamino carboxylic acid, the lactam thereof or monoamino carboxylic acid/lactam mixtures,

A2) 47.5 to 50 mol% of at least one primary or secondary diamine,

A3) 10 to 30 mol% of at least one dicarboxylic acid with sulfonate groups and, where appropriate,

A4) 20 to 40 mol% of at least one other dicarboxylic acid, where the total of the molar proportions of monomers A3) and A4) essentially corresponds to the molar proportion of monomer A2).

If present, the proportion of component A1 is at least 0.5 mol%.

Advantageous polyamides are obtainable from only monomers A2), A3) and A4) described above. In this case, the molar proportion of monomer A2) is 50 mol%. The molar proportions of monomers A3) and A4) vary within the limits stated above, with the total likewise being 50 mol%.

It is particularly advantageous if at least two different diamines are used to prepare the novel polymers.

Suitable monomers A1) are the monoamino carboxylic acids and their lactams known for preparing polyamides. They are preferably C_2-C_{12}-monoamino carboxylic acids and, in particular, monoamino carboxylic acids of the general formula H_2N-R^1-COOH, in which R^1 is a straight-chain or branched, saturated or unsaturated, aliphatic, cycloaliphatic or aromatic radical. Radicals R^1 of this type may also be substituted one or more times by groups selected independently from hydroxyl or C_{1-4}-alkoxy. Examples of suitable monoamino carboxylic acids and lactams are ω-aminoundecanoic acid, pyrrolidone, ε-caprolactam, laurolactam, caprylolactam or enantholactam.

Examples of suitable monomers A2) are primary C_2-C_{18}-diamines, in particular those of the formula H_2N-R^2-NH_2, in which R^2 is a straight-chain or branched, saturated and unsaturated, aliphatic radical having 2 to 18, preferably having 2 to 14, and in particular, having 5 to 11 carbon atoms, which may also be substituted one or more times by groups selected independently from hydroxyl or C_{1-4}-alkoxy, a saturated or unsaturated cycloaliphatic radical having 5 to 8 and preferably 6 carbon atoms, which may also be substituted one or more times by groups selected independently from hydroxyl, C_{1-4}-alkyl or C_{1-4}-alkoxy, a plurality of, and in particular two, cycloaliphatic radicals which are linked together and are of the type identified above, an aromatic radical having 6 to 18, preferably 6 to 12, carbon atoms and, in particular, a phenyl radical, which may also be substituted one or more times by groups selected independently from hydroxyl, C_{1-4}-alkyl or C_{1-4}-alkoxy, or a plurality of, and in particular two, aromatic radicals which are linked together and are of the type identified above. Aliphatic and cycloaliphatic radicals are preferred.

Cycloaliphatic or aromatic radicals which are linked together are linked together by either a bond or a divalent radical, it being possible for the divalent radical to be, in particular, a C_1-C_4-alkylene group such as a methylene, 1,1-, 1,2-ethylene, 1,1-, 1,2-, 1,3- and 2,2-propylene group, -O-, -S-, -SO_2-, C(O) and an alkylene group of the type identified above which is interrupted by -O-, -S-, -SO_2- or C(O).

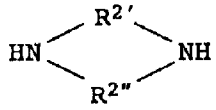
Aliphatic radicals are preferably alkylene or alkenylene groups which may also be interrupted one or more times by -O-, -S-, -SO_2- or C(O).

Cycloaliphatic radicals are preferably cycloalkyl or cycloalkenyl groups which may also be interrupted one or more times by -O-, -S-, $-SO_2-$ or C(O).

Examples of suitable primary diamines are alkylenediamines or cycloalkyldiamines such as 1,2-ethanediamine, 1,5-pentanediamine, di(4-aminocyclohexyl)methane, 2,2-di(4-aminocyclohexyl)propane, di(3-methyl-4-aminocyclohexyl)methane or, preferably, hexamethylenediamine. Also suitable are 2,2,4-trimethylhexamethylenediamine, 2-butyl-2-ethyl-1,5-pentanediamine, 2-methylpentamethylenediamine or 4,7-dioxadecane-1,10-diamine.

Also suitable as monomers A2) are secondary diamines, for example those derived from a primary diamine of the type described above by replacement of at least one amine hydrogen by a suitable substituent such as C_1-C_3-alkyl.

Preferred secondary diamines are cyclic diamines of the general formula



in which $R^{2'}$ and $R^{2''}$ may, independently of one another, have the meanings indicated above for R^2. An example of a diamine of this type is piperazine.

Suitable monomers A3) with sulfonate groups are those in which the sulfo group is in salt form, e.g. as salt of an alkali metal such as lithium, sodium or potassium, or of an ammonium group which is optionally substituted by one to 4 aliphatic or aromatic groups. Suitable monomers with sulfonate groups are sulfonic acid salts of C_4-C_{20}- and, preferably, C_4-C_{12}-dicarboxylic acids. Particularly suitable dicarboxylic acids are those of the general formula HOOC-R^3-COOH, in which R^3 may have the meanings mentioned above for R^2.

R^3 is preferably an aromatic radical. This includes phenyl, naphthyl or diphenyl radicals and two phenyl radicals linked together by a divalent radical. Examples of such divalent radicals are indicated above.

The sulfonate groups can be linked to R^3 directly or via a C_1-C_4-alkylene bridge. One example of aliphatic dicarboxylic acids with sulfonate groups is sulfosuccinic acid. Suitable aromatic dicarboxylic acids with sulfonate groups are based, for example, on phthalic acid, isophthalic acid, terephthalic acid, 1,4- and 2,6-naphthalenedicarboxylic acid, 3,3'- and 4,4'-diphenyldicarboxylic acid, 3,3'- and 4,4'-diphenylmethane-dicarboxylic acid or 2-phenoxyterephthalic acid. As a rule, the aromatic dicarboxylic acids have one or two sulfonate groups. These can be linked to any positions not substituted by carboxyl groups, directly, for example as in 5-sulfoisophthalic acid, or via a divalent bridge, for example as in 5-sulfopropoxy-isophthalic acid. A salt of 5-sulfoisophthalic acid, in particular the sodium salt, is particularly preferred.

Suitable and preferred monomers A4) are C_2-C_{16}-dicarboxylic acids and, in particular, dicarboxylic acids of the general formula HOOC-R^4-COOH. The definition of the radical R^3 applies in principle to the radical R^4 except that R^4 has no sulfonate group. Examples of aliphatic dicarboxylic acids are azelaic acid, dodecanedicarboxylic acid or, preferably, adipic acid or sebacic acid. Examples of suitable aromatic dicarboxylic acids are isophthalic acid or terephthalic acid, which may also be substituted, such as, for example, 3-tert-butylisophthalic acid, also 3,3'- or 4,4'-diphenyldicarboxylic acid, 3,3'- or 4,4'-diphenylmethanedicarboxylic acid, di(3- or 4-carboxyphenyl) sulfone, 1,4- or 2,6-naphthalenedicarboxylic acid or 2-phenoxyterephthalic acid.

It is of course true for all monomer groups that mixtures of the particular monomers can also be employed.

The polyamides with sulfonate groups can be prepared in a manner known per se.

The preferred mode of preparation which may be mentioned is the batch process (discontinuous mode of preparation). This entails the aqueous monomer solution being heated in an autoclave to temperatures from 240 to 300°C over the course of 0.5 to 3 h, during which a pressure of from 10 to 50 bar, in particular 15 to 30 bar, is reached and is kept constant for up to 4 h by releasing excess steam. The autoclave is then decompressed to atmospheric pressure at constant temperature within a period of from 0.5 to 3 h. The polymer melt is subsequently removed from

the autoclave, cooled with air or nitrogen and subsequently granulated.

The copolyamide obtained in this way usually has a viscosity number between 25 and 110 ml/g, preferably from 30 to 80 ml/g, measured on a 0.5% by weight solution in 96% strength sulfuric acid.

The copolymers generally have K values of at least 7, preferably 10 to 250. The polymers may have K values of up to 300. The K values are determined by the method of H. Fikentscher, Cellulosechemie, Volume 13, 58-64 and 71-74 (1932), in aqueous solution or in an organic solvent at 25°C and at concentrations which are between 0.1% and 5%, depending on the K value range.

Besides the polymeric binders described above, it is possible to employ in particular up to 30% by weight, based on the total weight of the binder, of other binders such as polymers, copolymers, cellulose derivatives, starch and starch derivatives. Suitable examples are:

Polyvinylpyrrolidone (PVP), copolymers of N-vinylpyrrolidone (NVP) and vinyl esters, especially vinyl acetate, copolymers of vinyl acetate and crotonic acid, partially hydrolyzed polyvinyl acetate, polyvinyl alcohol, polyvinylformamide, partially or completely hydrolyzed polyvinylformamide, poly(hydroxyalkyl acrylates), poly(hydroxyalkyl methacrylates), polyacrylates and polymethacrylates (Eudragit types), copolymers of methyl methacrylate and acrylic acid, polyacrylamides, polyethylene glycols, cellulose esters, cellulose ethers, especially methyl cellulose and ethyl cellulose, hydroxyalkylcelluloses, especially hydroxypropylcellulose, hydroxyalkylalkylcelluloses, especially hydroxypropylethylcellulose, cellulose phthalates, especially cellulose acetate phthalate and hydroxypropyl methylcellulose phthalate, and mannans, especially galactomannans. Of these, polyvinylpyrrolidone, copolymers of N-vinylpyrrolidone and vinyl esters, poly(hydroxyalkyl acrylates), poly(hydroxyalkyl methacrylates), polyacrylates, polymethacrylates, alkylcelluloses and hydroxyalkylcelluloses are particularly preferred.

The polymeric binder must soften or melt in the complete mixture of all the components in the range from 50 to 180°C, preferably 60 to 130°C. The glass transition temperature of the mixture must therefore be below 180°C, preferably below 130°C. If necessary, it is reduced by conventional pharmacologically acceptable plasticizing auxiliaries. The amount of plasticizer does not

exceed 30% of the total weight of binder and plasticizer in order to form storage-stable drug forms which show no cold flow. However, the mixture preferably contains no plasticizer.

Examples of such plasticizers are:

Long-chain alcohols, ethylene glycol, propylene glycol, glycerol, trimethylolpropane, triethylene glycol, butanediols, pentanols such as pentaerythritol, hexanols, polyethylene glycols, polypropylene glycols, polyethylene/propylene glycols, silicones, aromatic carboxylic esters (e.g. dialkyl phthalates, trimellitic esters, benzoic esters, terephthalic esters) or aliphatic dicarboxylic esters (e.g. dialkyl adipates, sebacic esters, azelaic esters, citric and tartaric esters), fatty acid esters such as glycerol mono-, di- or triacetate or sodium diethylsulfosuccinate. The concentration of plasticizer is generally from 0.5 to 15, preferably 0.5 to 5, % of the total weight of the mixture.

Conventional pharmaceutical auxiliaries, whose total amount can be up to 100% of the weight of the polymer, are, for example, extenders and bulking agents such as silicates or diatomaceous earth, magnesium oxide, aluminum oxide, titanium oxide, stearic acid or its salts, e.g. the magnesium or calcium salt, methyl cellulose, sodium carboxymethylcellulose, talc, sucrose, lactose, cereal or corn starch, potato flour, polyvinyl alcohol, in particular in a concentration of from 0.02 to 50, preferably 0.20 to 20, % of the total weight of the mixture.

Lubricants such as aluminum and calcium stearates, talc and silicones, in a concentration of from 0.1 to 5, preferably 0.1 to 3, % of the total weight of the mixture.

Flowability agents such as animal or vegetable fats, especially in hydrogenated form and those which are solid at room temperature. These fats preferably have a melting point of 50°C or above. Triglycerides of C_{12}, C_{14}, C_{16} and C_{18} fatty acids are preferred. It is also possible to use waxes such as carnauba wax. These fats and waxes may be admixed advantageously alone or together with mono- and/or diglycerides or phosphatides, especially lecithin. The mono- and diglycerides are preferably derived from the abovementioned fatty acid types. The total amount of fats, waxes, mono-, diglycerides and/or lecithins is from 0.1 to 30, preferably 0.1 to 5, % of the total weight of the composition for each layer.

Dyes, such as azo dyes, organic or inorganic pigments or dyes of

natural origin, with preference for inorganic pigments in a concentration of from 0.001 to 10, preferably 0.5 to 3, % of the total weight of the mixture.

Stabilizers such as antioxidants, light stabilizers, hydroperoxide destroyers, radical scavengers, stabilizers against microbial attack.

It is also possible to add wetting agents, preservatives, disintegrants, adsorbents, release agents dispersing additives, propellants and defoamers (cf., for example, H. Sucker et al., Pharmazeutische Technologie, Thieme-Verlag, Stuttgart 1978).

Auxiliaries include for the purpose of the invention substances for producing a solid solution of the active ingredient. Examples of these auxiliaries are pentaerythritol and pentaerythritol tetraacetate, polymers such as polyethylene oxides and polypropylene oxides and their block copolymers (poloxamers), phosphatides such as lecithin, homo- and copolymers of vinylpyrrolidone, surfactants such as polyoxyethylene 40 stearate, and citric and succinic acids, bile acids, sterols and others as indicated, for example, in J. L. Ford, Pharm. Acta Helv. 61 (1986) 69-88.

Auxiliaries are also regarded as being bases and acids added to control the solubility of an active ingredient (see, for example, K. Thoma et al., Pharm. Ind. 51 (1989) 98-101).

The only precondition for the suitability of auxiliaries is adequate thermal stability.

Active ingredients mean for the purpose of the invention all substances with a physiological effect as long as they do not decompose under the processing conditions. These are, in particular, pharmaceutical active ingredients (for humans and animals), active ingredients for plant treatment, insecticides, active ingredients of human and animal foods, fragrances and perfume oils. The amount of active ingredient per dose unit and the concentration may vary within wide limits depending on the activity and the release rate. The only condition is that they suffice to achieve the desired effect. Thus, the concentration of active ingredient can be in the range from 0.1 to 95, preferably from 20 to 80, in particular 30 to 70, % by weight. It is also possible to employ combinations of active ingredients. Active ingredients for the purpose of the invention also include vitamins and minerals. The vitamins include the vitamins of the A group, the B group, by which are meant besides B_1, B_2, B_6 and B_{12}

and nicotinic acid and nicotinamide also compounds with vitamin B properties such as adenine, choline, pantothenic acid, biotin, adenylic acid, folic acid, orotic acid, pangamic acid, carnitine, p-aminobenzoic acid, myo-inositol and lipoic acid, and vitamin C, vitamins of the D group, E group, F group, H group, I and J groups, K group and P group. Active ingredients for the purpose of the invention also include therapeutic peptides. Plant treatment agents include, for example, vinclozolin, epoxiconazole and quinmerac.

The novel process is suitable, for example, for processing the following active ingredients:

acebutolol, acetylcysteine, acetylsalicylic acid, aciclovir, alprazolam, alfacalcidol, allantoin, allopurinol, ambroxol, amikacin, amiloride, aminoacetic acid, amiodarone, amitriptyline, amlodipine, amoxicillin, ampicillin, ascorbic acid, aspartame, astemizole, atenolol, beclomethasone, benserazide, benzalkonium hydrochloride, benzocaine, benzoic acid, betamethasone, bezafibrate, biotin, biperiden, bisoprolol, bromazepam, bromhexine, bromocriptine, budesonide, bufexamac, buflomedil, buspirone, caffeine, camphor, captopril, carbamazepine, carbidopa, carboplatin, cefachlor, cefalexin, cefadroxil, cefazoline, cefixime, cefotaxime, ceftazidime, ceftriaxone, cefuroxime, selegiline, chloramphenicol, chlorhexidine, chlorpheniramine, chlortalidone, choline, cyclosporin, cilastatin, cimetidine, ciprofloxacin, cisapride, cisplatin, clarithromycin, clavulanic acid, clomipramine, clonazepam, clonidine, clotrimazole, codeine, cholestyramine, cromoglycic acid, cyanocobalamin, cyproterone, desogestrel, dexamethasone, dexpanthenol, dextromethorphan, dextropropoxiphene, diazepam, diclofenac, digoxin, dihydrocodeine, dihydroergotamine, dihydroergotoxin, diltiazem, diphenhydramine, dipyridamole, dipyrone, disopyramide, domperidone, dopamine, doxycycline, enalapril, ephedrine, epinephrine, ergocalciferol, ergotamine, erythromycin, estradiol, ethinylestradiol, etoposide, Eucalyptus globulus, famotidine, felodipine, fenofibrate, fenoterol, fentanyl, flavin mononucleotide, fluconazole, flunarizine, fluorouracil, fluoxetine, flurbiprofen, furosemide, gallopamil, gemfibrozil, gentamicin, Gingko biloba, glibenclamide, glipizide, clozapine, Glycyrrhiza glabra, griseofulvin, guaifenesin, haloperidol, heparin, hyaluronic acid, hydrochlorothiazide, hydrocodone, hydrocortisone, hydromorphone, ipratropium hydroxide, ibuprofen, imipenem, indomethacin, iohexol, iopamidol, isosorbide dinitrate, isosorbide mononitrate, isotretinoin, ketotifen, ketoconazole, ketoprofen, ketorolac, labetalol, lactulose, lecithin, levocarnitine, levodopa, levoglutamide,

levonorgestrel, levothyroxine, lidocaine, lipase, imipramine, lisinopril, loperamide, lorazepam, lovastatin, medroxy progesterone, menthol, methotrexate, methyldopa, methyl prednisolone, metoclopramide, metoprolol, miconazole, midazolam, minocycline, minoxidil, misoprostol, morphine, multivitamin mixtures or combinations and mineral salts, N-methylephedrine, naftidrofuryl, naproxen, neomycin, nicardipine, nicergoline, nicotinamide, nicotine, nicotinic acid, nifedipine, nimodipine, nitrazepam, nitrendipine, nizatidine, norethisterone, norfloxacin, norgestrel, nortriptyline, nystatin, ofloxacin, omeprazole, ondansetron, pancreatin, panthenol, pantothenic acid, paracetamol, penicillin G, penicillin V, phenobarbital, pentoxifylline, phenoxymethylpenicillin, phenylephrine, phenylpropanolamine, phenytoin, piroxicam, polymyxin B, povidone-iodine, pravastatin, prazepam, prazosin, prednisolone, prednisone, bromocriptine, propafenone, propranolol, proxyphylline, pseudoephedrine, pyridoxine, quinidine, ramipril, ranitidine, reserpine, retinol, riboflavin, rifampicin, rutoside, saccharin, salbutamol, salcatonin, salicylic acid, simvastatin, somatropin, sotalol, spironolactone, sucralfate, sulbactam, sulfamethoxazole, sulfasalazine, sulpiride, tamoxifen, tegafur, teprenone, terazosin, terbutaline, terfenadine, tetracycline, theophylline, thiamine, ticlopidine, timolol, tranexamic acid, tretinoin, triamcinolone acetonide, triamterene, trimethoprim, troxerutin, uracil, valproic acid, vancomycin, verapamil, vitamin E, folinic acid, zidovudine.

Preferred active ingredients are ibuprofen (as racemate, enantiomer or enriched enantiomer), ketoprofen, flurbiprofen, acetylsalicylic acid, verapamil, paracetamol, nifedipine or captopril.

To produce the solid dosage forms, a plastic mixture of the components (melt) is prepared and then subjected to a shaping step. There are various ways of mixing the components and forming the melt. The mixing can take place before, during and/or after the formation of the melt. For example, the components can be mixed first and then melted or be mixed and melted simultaneously. The plastic mixture is often then homogenized in order to disperse the active ingredient thoroughly.

However, it has proven preferable, especially when sensitive active ingredients are used, first to melt the polymeric binder and, where appropriate, make a premix with conventional pharmaceutical additives, and then to mix in (homogenize) the sensitive active ingredient(s) in the plastic phase in intensive mixers with very short residence times. The active ingredient(s)

can for this purpose be employed in solid form or in solution or dispersion.

The components are generally employed as such in the production process. However, they can also be used in liquid form, i.e. as solution, suspension or dispersion.

Suitable solvents for the liquid form of the components are primarily water or a water-miscible organic solvent or a mixture thereof with water. However, it is also possible to use organic solvents which are immiscible or miscible with water. Suitable water-miscible solvents are, in particular, C_1-C_4-alkanols such as ethanol, isopropanol or n-propanol, polyols such as ethylene glycol, glycerol and polyethylene glycols. Suitable water-immiscible solvents are alkanes such as pentane or hexane, esters such as ethyl acetate or butyl acetate, chlorinated hydrocarbons such as methylene chloride, and aromatic hydrocarbons such as toluene and xylene. Another solvent which can be used is liquid CO_2.

The solvent used in the individual case depends on the component to be taken up and the properties thereof. For example, pharmaceutical active ingredients are frequently used in the form of a salt which is, in general, soluble in water. Water-soluble active ingredients can therefore be employed as aqueous solution or, preferably, be taken up in the aqueous solution or dispersion of the binder. A corresponding statement applies to active ingredients which are soluble in one of the solvents mentioned, if the liquid form of the components used is based on an organic solvent.

It is possible where appropriate to replace melting by dissolving, suspending, or dispersing in the abovementioned solvents, if desired and/or necessary with the addition of suitable auxiliaries such as emulsifiers. The solvent is then generally removed to form the melt in a suitable apparatus, e.g. an extruder. This will be comprised by the term mixing hereinafter.

The melting and/or mixing takes place in an apparatus customary for this purpose. Particularly suitable ones are extruders or containers which can be heated where appropriate and have an agitator, e.g. kneaders (like those of the type to be mentioned below).

A particularly suitable mixing apparatus is one employed for mixing in plastics technology. Suitable apparatuses are

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solvent, the extruders are generally equipped with an evaporating section. Particularly preferred extruders are those of the ZKS series from Werner & Pfleiderer.

It is also posible according to the invention to produce multilayer pharmaceutical forms by coextrusion, in which case a plurality of mixtures of the components described above is fed together to an extrusion die so as to result in the required layered structure of the multilayer pharmaceutical form. It is preferable to use different binders for different layers.

Multilayer drug forms preferably comprise two or three layers. They may be in open or closed form, in particular as open or closed multilayer tablets.

At least one of the layers contains at least one pharmaceutical active ingredient. It is also possible for another active ingredient to be present in another layer. This has the advantage that two mutually incompatible active ingredients can be processed or that the release characteristics of the active ingredient can be controlled.

The shaping takes place by coextrusion with the mixtures from the individual extruders or other units being fed into a common coextrusion die and extruded. The shape of the coextrusion die depends on the required pharmaceutical form. Examples of suitable dies are those with a flat orifice, called slit dies, and dies with an annular orifice. The design of the die depends on the polymeric binder used and the required pharmaceutical form.

The resulting mixture is preferably solvent-free, i.e. it contains neither water nor an organic solvent.

The plastic mixture is, as a rule, subjected to final shaping. This can result in a large number of shapes depending on the die and mode of shaping. For example, if an extruder is used, the extrudate can be shaped between a belt and a roll, between two belts or between two rolls, as described in EP-A-358 105, or by calendering in a calender with two molding rolls, see, for example, EP-A-240 904. Other shapes can be obtained by extrusion and hot- or cold-cut of the extrudate, for example small-particle and uniformly shaped pellets. Hot-cut pelletization usually results in lenticular dosage forms (tablets) with a diameter of from 1 to 10 mm, while cold-cut pelletization normally results in cylindrical products with a length to diameter ratio of from 1 to 10 and a diameter of from 0.5 to 10 mm. It is thus possible to produce monolayer but also, on use of coextrusion, open or closed

multilayer dosage forms, for example oblong tablets, coated tablets, pastilles and pellets. The resulting granules can also be ground to a powder and compressed to tablets in a conventional way. Micropastilles can be produced by the Rotoform-Sandvik process. These dosage forms can be rounded and/or provided with a coating by conventional methods in a subsequent process step. Examples of materials suitable for film coatings are polyacrylates such as the Eudragit types, cellulose esters such as the hydroxypropylcellulose phthalates, and cellulose ethers such as ethylcellulose, hydroxypropylmethylcellulose or hydroxypropylcellulose.

In specific cases there may be formation of solid solutions. The term solid solutions is familiar to the skilled worker, for example from the literature cited at the outset. In solid solutions of active ingredients in polymers, the active ingredient is in the form of a molecular dispersion in the polymer.

The following examples are intended to illustrate the novel process without restricting it, however.

Example 1

520 g of a polyamide from 16.67 mol% of sodium 5-sulfoisophthalic acid, 16.67 mol% of isophthalic acid, 33.33 mol% of hexamethylenediamine and 33.33% of ε-caprolactam (K value 21.0; 1% strength in dimethylformamide; M_n (end group analysis): 6000-7000; T_g = 149°C) are extruded with 480 g of verapamil hydrochloride under the conditions indicated hereinafter and calendered to give 500 mg oblong tablets by the process described in EP-A-240 904.

Section 1: 94°C
Section 2: 150°C
Section 3: 123°C
Section 4: 100°C
Section 5: 81°C
Dye: 79°C

The release after 8 h was 10% [USP paddle method (pH change)].

We claim:

1. A process for producing solid dosage forms by mixing at least one polymeric binder, where appropriate at least one active ingredient and, where appropriate, conventional additives to form a plastic mixture, and shaping, wherein polyamides with sulfonate groups are used as polymeric binder.

2. A process as claimed in claim 1, wherein the polyamide with sulfonate groups is obtainable from

A1) 0 to 90 mol%, preferably 0 to 50 mol%, particularly preferably 0 to 45 mol%, of at least one monoamino carboxylic acid, the lactam thereof or monoamino carboxylic acid/lactam mixtures,

A2) 5 to 50 mol%, preferably 45 to 50 mol%, particularly preferably 47.5 to 50 mol%, of at least one primary or secondary diamine,

A3) 0.5 to 49.5 mol%, preferably 5 to 35 mol%, particularly preferably 10 to 30 mol%, of at least one dicarboxylic acid with sulfonate groups and, where appropriate,

A4) 0.5 to 49.5 mol%, preferably 15 to 45 mol%, particularly preferably 20 to 40 mol%, of at least one other dicarboxylic acid,

where the total of the molar proportions of monomers A3) and A4) essentially corresponds to the molar proportion of monomer A2).

3. A process as claimed in either of claims 1 or 2, wherein the monomers A2) comprise at least two different diamines.

4. A process as claimed in any of the preceding claims, wherein the dicarboxylic acid with sulfonate groups is the sodium salt of 5-sulfoisophthalic acid.

5. A process as claimed in any of the preceding claims, wherein the formation of the plastic mixture takes place by mixing and/or melting the components in an extruder.

6. A process as claimed in any of claims 1 to 5 for producing dosage forms containing pharmaceutical active ingredients.

7. A process as claimed in any of claims 1 to 5 for producing plant treatment compositions.

8. A process as claimed in any of claims 1 to 5 for producing animal food additives and supplements.

9. A process as claimed in any of claims 1 to 5 for producing human food supplements.

10. A solid dosage form obtainable by a process as claimed in any of claims 1 to 9.